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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/022,618	12/17/2001	Guido Henning	Le A 35 010	1214

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EXAMINER

UNGAR, SUSAN NMN

ART UNIT PAPER NUMBER

1642

DATE MAILED: 12/14/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/022,618	HENNING ET AL.	
	Examiner	Art Unit	
	Susan Ungar	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on 6/15/06, 8/3/06.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☐ Claim(s) 1, 3-5, 12 and 15 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☐ Claim(s) 1, 3-5, 12 and 15 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>6/28/06, 7/17/06, 12/19/03</u> . | 6) <input type="checkbox"/> Other: _____ |

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed June 15, 2006 is acknowledged and has been entered. Applicant's submission filed on August 3, 2006 is acknowledged and has been entered. Claims 2, 6-11 have been canceled, claims 1, 3-5 have been amended, claims 12-15 have been added and 15 has been amended. An action on the RCE follows.
2. Claims 1, 3-5, 12-15 are pending and currently under examination.
3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.
4. The following rejections are being maintained with new grounds of rejection added for newly added claims:

Claim Rejections - 35 USC 103

5. Claims 1, 3, 5 remain rejected under 35 USC 103 and newly added claims 12, 15 are rejected under 35 USC 103 for the reasons previously set forth in the paper mailed March 15, 2006, Section 5, pages 2-6.

Applicant reiterates the teachings of Pillai and argues that Pillai does not contemplate at least two features of the presently claimed methods, in particular (a) Pillai does not employ at least two molecular markers of cervical cancer that are simultaneously detected, (b) Pillai does not contemplate combining color signal intensities and does not contemplate measuring and accrediting the combined color signal intensities to achieve detection. At best, Pillai et al disclose only a manual method to estimate cancer risk through subjective consideration of separately

obtained fluorescence data. The arguments have been considered but has not been found persuasive because Applicant is arguing the individual reference without clearly addressing the combined teachings. It must be remembered that the references are relied upon in combination and are not meant to be considered separately as in a vacuum. It is the combination of all of the cited and relied upon references which made up the state of the art with regard to the claimed invention. Applicant's claimed invention fails to patentably distinguish over the state of the art represented by the cited references taken in combination. In re Young, 403 F.2d 754, 159 USPQ 725 (CCPA 1968); In re Keller 642 F.2d 413, 208 USPQ 871 (CCPA 1981).

Applicant argues that the combination with Geiger et al or Giuliano et al with Pillai do not cure the deficiencies of Pillai et al. Applicant reiterates the teachings of Geiger et al and Giuliano et al and argues that nowhere do Geiger et al or Giuliano et al, either alone or in combination, contemplate the particular features of the claimed methods, including detection of two markers of cervical cancer simultaneously and combining their color signals which are then accredited to detect tumor cells and their precursors in a uterine cervical smear. The argument has been considered but has not been found persuasive because once again, Applicant is arguing individual references, that is Geiger et al and Giuliano et al in combination without clearly addressing the fully combined teachings. It must be remembered that the references are relied upon in combination and are not meant to be considered separately as in a vacuum. It is the combination of all of the cited and relied upon references which made up the state of the art with regard to the claimed invention. Applicant's claimed invention fails to patentably distinguish over the state of the art represented by the cited references taken in

combination. In re Young, 403 F.2d 754, 159 USPQ 725 (CCPA 1968); In re Keller 642 F.2d 413, 208 USPQ 871 (CCPA 1981).

Applicant goes into detail drawn to Giuliano et al, wherein Applicant reiterates that (a) Guiliano et al does not relate to cancer diagnosis, but rather to the effects of candidate drugs on complex molecular events in a cell, (b) the fluorescence signals of the nucleus and the antibody-labeled translocation protein are not combined, (c) the fluorescence measurements are measured separated and never at any point combined in the way claimed by the present methods. The arguments have been considered but have not been found persuasive because (a') Applicant is once again arguing the references individually without clearly addressing the combined teachings. It must be remembered that the references are relied upon in combination and are not meant to be considered separately as in a vacuum. It is the combination of all of the cited and relied upon references which made up the state of the art with regard to the claimed invention. (b') although the fluorescence's of the two regions are not combined, the fluorescence's within each of the two regions are clearly combined. The test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference and it is not that the claimed invention must be expressly suggested in any one or all of the references; but rather the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981), (c') a review of the claims does not reveal any particular method of combination claimed by the present methods and contrary to Applicant's arguments, Guiliano specifically teaches not only separate measurements but also the combination of

the measurements wherein at the paragraph bridging columns 18-19 the Guiliano specifically teaches the measurement “for the combined colors”.

Applicant argues that the Giuliano et al disclosed methods teach away from the presently claimed methods because the nature of the type of data obtained by Giuliano et al would not be feasible if the claims steps of detecting color signal intensities and measuring and accrediting the combined color signal intensities were carried out. The argument has been considered but has not been found persuasive because the instantly claimed method is specifically drawn to detecting tumor cells in a cervical cancer smear and using the method for diagnosis is not only inferred by the claims, contemplated by the specification but also is specifically claimed in newly added claim 14 which will be rejected under 35 USC 103 below. Although Applicant argues that that the methods of Giuliano et al cannot be used for the instant diagnostic assay, this in fact is not the case. In particular, Giuliano et al specifically teach that “In addition to drug screening applications, the present invention may be applied to clinical diagnostics” (see the section immediately preceding “Image Analysis and Acquisition).

Applicant argues that Guiliano et al requires substantial subjective analysis in its methods given that the specification states that as a final phase, data should be examined by the user of the method. The argument has been considered but has not been found persuasive because Applicant is mischaracterizing the teachings of Guiliano et al. In point of fact Guiliano teaches that “As a final phase of a complete scan, reports can be generated on one or more statistics of the measured features. Users can generate a graphical report of data summarized on a well-by-well basis for the scanned region of the plate using an interactive report generation procedure 120. This report includes a summary of the statistics by well in tabular

and graphical format and identification information on the sample. The report window allows the operator to enter comments about the scan for later retrieval. Multiple reports can be generated on many statistics and be printed with the touch of one button. Reports can be previewed for placement and data before being printed.” Nowhere is substantial subjective analysis required.

Applicant argues that Examiner uses improper hindsight reasoning. The argument has been considered but has not been found persuasive because it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. In re McLaughlin , 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). Thus, although some degree of hindsight is permissible in making rejections under 35 USC 103, methods of detecting tumor cells and their precursor cells in uterine cervical smears comprising detecting markers with color marked reagents that specifically bind to at least two molecular markers/three detectable markers of cervical cancer, wherein the markers are Bcl-2, HPV-16 E6, p53 were well known in the art at the time the invention was made as taught by Pillai et al and the conventional use of triple immunofluorescence microscopy was well known in the art at the time the invention was made as taught by US 20020045591 and the efficiency of automated methods for combining the color signal intensities, measuring and accrediting the combined color signal intensities and thereby detecting molecules within cells were well known in the art at the time the invention was made as taught by US Patent 6,756,207. Contrary to the assertion of Applicant that Examiner uses impermissible hindsight, it is clear

that the combined references teach not only the suggestion but also the means and motivation to make the claimed method that is to successfully detect tumor cells and their precursor cells in uterine cervical cancer by contacting the cells with color marked reagents that specifically bind to at least two/three molecular markers of cervical cancer, simultaneously detect color signal intensities from said markers, combine the color signal intensities and measure and accredit the combined color signal intensities, thereby detecting tumor cells and their precursor cells in uterine cervical smears. The test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference and it is not that the claimed invention must be expressly suggested in any one or all of the references; but rather the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). For the reasons set forth previously and above, the claimed invention is obvious over the combined references.

The arguments have been carefully considered but have not been found persuasive and the rejection is maintained.

6. Claims 1 and 4 remain rejected and newly added claim 13 is rejected under 35 USC 103 for the reasons previously set forth in the paper mailed March 15, 2006, Section 5, pages 6-8.

Applicant argues that taking the cited references in further combination with Kihana et al, the combination still falls short of the claimed methods. Applicant reiterates the teachings of Kihana and argues that Kihana et al does not teach or suggest any of the features of the presently claimed methods, that is detection of at least two markers of cervical cancer simultaneously and accrediting color signal intensities obtained from the simultaneous detection of the markers. The arguments

have been considered but have not been found persuasive because once again, Applicant is arguing the reference individually without clearly addressing the combined teachings. It must be remembered that the references are relied upon in combination and are not meant to be considered separately as in a vacuum. It is the combination of all of the cited and relied upon references which made up the state of the art with regard to the claimed invention.

Applicant argues that Examiner uses improper hindsight reasoning. The argument has been considered but has not been found persuasive because it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. In *re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). Thus, although some degree of hindsight is permissible in making rejections under 35 USC 103, methods of detecting tumor cells and their precursor cells in uterine cervical smears comprising detecting markers with color marked reagents that specifically bind to at least two molecular markers of cervical cancer, including p53, were well known in the art at the time the invention was made as taught by Pillai et al, and methods of detecting molecular marker of cervical cancer, that is c-erb-2, were well known in the art at the time the invention was made as taught by Kihana et al and further it was clear that motivation existed for combining the methods of Kihana et al for the reasons of record and the efficiency of automated methods for combining the color signal intensities, measuring and accrediting the combined color signal intensities and thereby detecting molecules within cells were well known in the art at the time the

invention was made as taught by US Patent 6,756,207. Contrary to the assertion of Applicant that Examiner uses impermissible hindsight, it is clear that the combined references teach not only the suggestion but also the means and motivation to make the claimed method that is to successfully detect tumor cells and their precursor cells in uterine cervical cancer by contacting the cells with color marked reagents that specifically bind to at least two molecular markers of cervical cancer, simultaneously detect color signal intensities from said markers, combine the color signal intensities and measure and accredit the combined color signal intensities, thereby detecting tumor cells and their precursor cells in uterine cervical smears. The test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference and it is not that the claimed invention must be expressly suggested in any one or all of the references; but rather the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). For the reasons set forth previously and above, the claimed invention is obvious over the combined references.

The arguments have been carefully considered but have not been found persuasive and the rejection is maintained.

New Grounds of Rejection

Claim Rejections - 35 USC 103

7. Claim 14 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Pillai et al, of record in view of US 20020045591, of record and US Patent No. 6,756,207 of record.

The claim is drawn to a method for detecting tumor cells and their precursors in uterine cervical smears by simultaneously detecting at least two polypeptide molecular markers in a cell or tissue sample comprising contacting the

cell or tissue sample with color marked reagents that specifically bind said molecular markers, simultaneously detecting signal intensities of color mixtures resulting from markers and combining and accrediting the signal intensities (claim 1), said method further comprising automated diagnosis using a diagnostic expert system (claim 14).

Pillai et al, US 20020045591, teach as set forth above. US Patent No. 6,756,207 teaches as set forth above and further teaches that "the present invention may be applied to clinical diagnostics" (see the section immediately preceding "Image Analysis and Acquisition).

It is noted that the specification defines "diagnostic expert system" as encompassing computer software which converts the image information into a proposed diagnosis (para 0024 of the published application).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have included in the automated method of the combined references, an automated method of diagnosis. Given that the system is automated, given that the system includes software that consolidates the information available, given the specific teaching of using the method for automated clinical diagnosis, it is *prima facie* obvious that the system encompasses a diagnostic expert system/software to provide said diagnosis. One would have been motivated to use the diagnostic capabilities of the system in order to provide a diagnosis of cancer/no cancer as inferred by the claim and contemplated by the specification as originally filed.

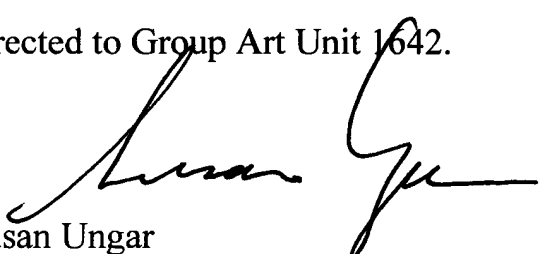
8. No claims allowed.

9. All other objections and rejections set forth in the previous office action are hereby withdrawn.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is (571) 272-0837. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew, can be reached at 571-272-0787. The fax phone number for this Art Unit is (571) 273-8300.

Effective, February 7, 1998, the Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1642.



Susan Ungar
Primary Patent Examiner
October 4, 2006